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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/623,329	11/13/2000	Marcel Bartolina Hendrikus Johannes Vervoort M.B.H.J.	T/98362 US	3850

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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/623,329	VERVOORT M.B.H.J. ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *15-18 and 27* is/are allowed.

6)☒ Claim(s) *16,19 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to Paper No. 17, filed December 3, 2002. Applicants amendments and arguments presented in the response of Paper No. 17 have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. This application contains subject matter in claims 32 and 33, drawn to an invention nonelected with traverse in Paper No. 14. In the response of Paper No. 17, Applicants state that the sequences of SEQ ID NO: 22 and 25 would not be removed from the claims because if claim 19 is allowable, claim 32 would also be allowable. However, the requirement to elect 6 sequences (2 sets of primers and 2 probes) was a restriction requirement and should not be construed as an election of species. Claim 19 is not allowable as detailed below and the sequences of SEQ ID NO:22 and 25 will not be examined herein.

A complete reply to the final rejection must include cancellation of nonelected subject matter or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 is indefinite over the phrase "substantially complementary". The specification does not provide a definition for this phrase and there is no art recognized definition for the term "substantially". Accordingly, it is unclear as to what level of complementarity would be encompassed by "substantially complementary".

This rejection was previously applied to claim 25. While claim 25 has been canceled, claim 28 has been newly added and includes the language "substantially complementary". Applicants state that because those of skill in the art recognize that the function of a probe is to hybridize to a target, one of skill in the art would be able to determine what is intended to be encompassed by "substantially complementary." However, probes are utilized under specific hybridization conditions and the degree of complementarity and the hybridization conditions determine the ability of a probe to bind to a target nucleic acid and the specificity at which the probe binds. The phrase "substantially complementary" does not allow one of skill in the art to determine whether the claims are intended to include any hybridization conditions, any degree of complementarity and any degree of specificity of binding. Probes are not all equivalent in terms of their function and thereby the recitation of "substantially complementary" does not allow one of skill in the art to determine the meets and bounds of the claimed invention.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Myers (GenBank Accession No.G34340).

Myers teaches a primer of 20 nucleotides consisting of the sequence of 5'-GGCTGTCACCCAGGTAGAAA-3'. The primer comprises 10 nucleotides of SEQ ID NO: 23 (i.e., nucleotides GGCTGTCACC). The claims are inclusive of sequences sharing any level of sequence complementarity with a 15 mer fragment of the oligonucleotide of SEQ ID NO: 23 and the primers of Myers share some level of sequence complementarity with said oligonucleotides. This rejection may be overcome by amendment of the claim to recite "and sequences fully complementary thereto".

In the response of Paper No. 17, it is stated that "Applicants respectfully disagree with this rejection which has absolutely no basis in the understanding of those skilled in the art regarding the meaning of the term "complementary". This argument has been fully considered but is not persuasive because Applicants have not provided any evidence as to what all practioners in the art consider to be included by the term "complementary". This term is not defined in the specification and in the art the term is used to refer to levels of complementarity ranging from 1% to 100%. The claims are not limited to any particular level of complementarity and thereby the claimed oligonucleotides may share any level of complementarity with the sequences from 165504 to 166166 of BARF1 and with SEQ ID NO: 23.

5. Claim 19 is rejected under 35 U.S.C. 102(a) as being anticipated by Myers (GenBank Accession No.G29936). This rejection now applies to amended claim 24.

Myers teaches a primer consisting of 5'-TTTAAACTGGTAGGAAACTAGGTG-3'. The primer comprises at least 10 nucleotides of SEQ ID NO: 26 (i.e., nucleotides TTTAAACTGG).

Accordingly, Myers teaches a primer/oligonucleotide comprising at least 15 nucleotides within the sequence of nucleotides 165504-166166 of BARF-1.The claims are inclusive of sequences sharing any level of sequence complementarity to an oligonucleotide comprising 15-35 nucleotides of 165504-166166 of BARF-1 and the primers of Myers share some level of sequence complementarity with said oligonucleotides.

In the response of Paper No. 17, Applicants state that this rejection has been overcome by amendment of the claim to recite fragments of at least 15 nucleotides. However, the claims have also been amended to include oligonucleotides sharing any level of sequence complementarity to at least 15 nucleotides within the sequence of nucleotides 165504-166166 of BARF-1 or 15 nucleotides of SEQ ID NO: 26. As discussed above, the claims include sequences which share 1% to 100% complementarity with at least 15 nucleotides within the sequence of nucleotides 165504-166166 of BARF-1 or 15 nucleotides of SEQ ID NO: 26 and thereby the claims are inclusive of the oligonucleotides of Myers

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> This application currently names joint inventors.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Myers (GenBank Accession No.G29936) in view of Mullis. It is noted that this rejection was previously applied to claim 24. In view of the amendment to claim 24, the rejection has been obviated. However, the rejection now applies to newly added claim 34.

Myers teaches a primer consisting of 5'-TTTAAACTGGTAGGAAACTAGGTG-3'. The primer comprises at least 10 nucleotides of SEQ ID NO: 26 (i.e., nucleotides TTTAAACTGG). Accordingly, Myers teaches a primer/oligonucleotide comprising at least 10 nucleotides within the sequence of nucleotides 165504-166166 of BARF-1. The claims as amended are inclusive of sequences sharing any level of sequence complementarity to an oligonucleotide comprising 15-35 nucleotides of 165504-166166 of BARF-1 and with SEQ ID NO: 26 and the primers of Myers share some level of sequence complementarity with said oligonucleotides. Myers does not teach labeling the oligonucleotide primer.

Mullis (e.g., column 23) teaches labeling primers for use in PCR in order to facilitate the detecting of PCR amplification products.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have labeled the primers of Myers in order to have achieved the benefits of facilitating the detection of the PCR amplification products.

In the response of Paper No. 17, Applicants traverse this rejection for the same reasons stated in paragraph 5 above. Accordingly, the response to those arguments presented in paragraph 5 above apply equally to the present grounds of rejection.

7. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Myers (GenBank Accession No.G34340) in view of Klevits.

Myers teaches a primer of 20 nucleotides consisting of the sequence of 5'-GGCTGTCACCCAGGTAGAAA-3'. The primer comprises 10 nucleotides of SEQ ID NO: 23 (i.e., nucleotides GGCTGTCACC). The claims are inclusive of sequences sharing any level of sequence complementarity to the oligonucleotide of SEQ ID NO: 23 and the primers of Myers share some level of sequence complementarity with said oligonucleotides. This rejection may be overcome by amendment of the claim to recite "and sequences fully complementary thereto". Myers does not teach incorporating a T7 polymerase promoter sequence into said primers.

Kievits teaches methods for amplifying nucleic acids by an isothermal enzymatic process referred to as NASAB. In this method, the primers are modified to include, at their 5' terminus, a T7 polymerase promoter sequence.

In view of the teachings of Kievits, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Myers so as to have

included a T7 polymerase promoter at the 5' terminus in order to have generated primers which could be used to effectively amplify target nucleic acids by the NASAB method.

In the response of Paper No. 17, Applicants traverse this rejection for the same reasons stated in paragraph 4 above. Accordingly, the response to those arguments presented in paragraph 4 above apply equally to the present grounds of rejection.

8. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Myers (GenBank Accession No.G29936) in view of Kievits.

Myers teaches a primer consisting of 5'-TTTAAACTGGTAGGAAACTAGGTG-3'. The primer comprises at least 10 nucleotides of SEQ ID NO: 26 (i.e., nucleotides TTTAAACTGG). Myers does not teach incorporating a T7 polymerase promoter sequence into said primers.

Kievits teaches methods for amplifying nucleic acids by an isothermal enzymatic process referred to as NASAB. In this method, the primers are modified to include, at their 5' terminus, a T7 polymerase promoter sequence.

In view of the teachings of Kievits, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Myers so as to have included a T7 polymerase promoter at the 5' terminus in order to have generated primers which could be used to effectively amplify target nucleic acids by the NASAB method.

In the response of Paper No. 17, Applicants traverse this rejection for the same reasons stated in paragraph 5 above. Accordingly, the response to those arguments presented in paragraph 5 above apply equally to the present grounds of rejection.

9. Claims 19, 20, 24, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over NCBI (Accession No. M80517) in view of Zhang et al (reference "AQ") and Cheung et al. This rejection now applies to newly added claim 28, 32 and 34.

This rejection applies to the claims as they are broadly drawn to primers and probes of 15-35 nucleotides comprising 15 mer fragments and sequences complementary or substantially complementary thereto.

NCBI teaches the complete sequence of the EBV genome, including the BARF-1 open reading frame. NCBI does not teach primers and probes from within the BARF-1 open reading frame.

Zhang et al teaches methods for detecting BARF-1 nucleic acids wherein probes to the BARF-1 nucleic acids are utilized. The probes of Zhang comprise the complete BARF-1 sequence and are labeled with a detectable moiety (page 155-156). Zhang teaches that expression of BARF-1 is correlated with the occurrence of lymphomas (see, e.g. Table 2).

Cheung teaches methods for detecting EBV nucleic acids wherein the methods comprise amplifying the EBV nucleic acids using primers in a polymerase chain reaction and then detecting the amplified nucleic acids using a labeled probe. The primers and probes exemplified by Cheung are 19-21 nucleotides in length.

In view of the teachings of Zhang and Cheung, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated additional probes to the EBV BARF-1 sequences and to have generated primers for amplifying BARF-1 sequences in

order to have provided an effective means for amplifying and detecting the expression of BARF-1 sequences. In the absence of unexpected results, all oligonucleotides from within the BARF-1 open reading frame are considered to provide equally effective primers and probes. Given the high level of skill in the art and the general information in the art as to how to readily generate primers and probes, particularly EBV primers and probes, it would have been obvious to one of ordinary skill in the art and well within the skill of the art at the time the invention was made to have generated primers and probes identical and equivalent to the broadly claimed primers and probes that could be used to amplify and detect BARF-1 expression. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers and probes in a kit for the benefits of convenience and cost-effectiveness for practioners in the art wishing to analyze BARF-1 expression.

In the response of Paper No. 17, Applicants traverse this rejection by stating that the cited references do not provide the motivation to select amplification primers or probes to the recited open reading frame of the BARF-1 region. This argument is not convincing because the claims are not limited to primers or probes consisting of specific sequences of the BARF-1 open reading frame. Rather, the claims are inclusive of primers or probes sharing any level of sequence complementarity to the BARF-1 sequences and to primers and probes comprising 10 to 15 nucleotides of BARF-1 fragments and sequences complementary thereto. The teachings in the cited art lead the ordinary artisan to the broadly claimed primers and probes and provide the motivation to generate such primers and probes for the general detection of BARF-1 sequences.

10. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over NCBI (Accession No. M80517) in view of Zhang et al (reference "AQ") and Cheung et al and further in view of Kievits. This rejection now applies to newly added claim 33 and claim 23 as amended.

The teachings of NCBI, Zhang and Cheung are presented above. The combined references do not teach incorporating a T7 polymerase promoter sequence into said primers.

Kievits teaches methods for amplifying nucleic acids by an isothermal enzymatic process referred to as NASAB. In this method, the primers are modified to include, at their 5' terminus, a T7 polymerase promoter sequence.

In view of the teachings of Kievits, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the BARF-1 primers so as to have included a T7 polymerase promoter at the 5' terminus in order to have generated primers which could be used to effectively amplify EBV BARF-1 target nucleic acids by the NASAB method

In the response of Paper No. 17, Applicants state that there is no suggestion in the prior art that the BARF-1 region may be used as a diagnostic tool to identify EBV-positive NPC and gastric carcinoma. This argument is not persuasive because the claims are drawn to products and not to methods for identifying EBV-positive NPC and gastric carcinoma. The claims are not limited to any specific primer or probe which detects EBV-positive NPC and gastric carcinoma and the claims do not define the oligonucleotides in terms of any structural limitation that would distinguish the claimed invention over the teachings in the cited prior art which lead the ordinary artisan to BARF-1 primers and probes.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

11. Claims 25, 28, 29, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over NCBI (Accession No. U21195) in view of Cheung and Zhang et al (reference "AQ").

This rejection applies to the claims as they are broadly drawn to primers and probes of 15-35 nucleotides comprising 15 mer fragments and sequences complementary or substantially complementary thereto.

NCBI teaches the sequences of the EBNA-1 gene, including the sequences comprising 10 to 15 mer fragments of present SEQ ID NO: 2, 3 and 5 and sequences sharing any level of sequence complementarity thereto. NCBI does not teach primers and probes from within the EBNA-1 gene.

Cheung teaches methods for detecting EBV nucleic acids wherein the methods comprise amplifying the EBV nucleic acids using primers in a polymerase chain reaction and then detecting the amplified nucleic acids using a labeled probe. The primers and probes exemplified by Cheung are 19-21 nucleotides in length. Cheung teaches primers and probes that amplify and detect BKRF1 (EBNA-1) sequences.

Zhang et al teaches methods for detecting EBV nucleic acids using probes to EBV nucleic acid sequences. Zhang also teaches labeling probes with a detectable moiety. The reference further teaches that EBNA1 is a latent protein and that detection of EBNA1 can be used to detect the presence of EBV (see, for example, page 154).

In view of the teachings of Cheung and Zhang, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated additional probes to the EBV BARF-1 sequences and to have generated primers for amplifying EBNA-1 sequences in order to have provided an effective means for amplifying and detecting the expression of EBNA-1 sequences. In the absence of unexpected results, all oligonucleotides from within the EBNA-1 gene are considered to provide equally effective primers and probes. Given the high level of skill in the art and the general information in the art as to how to readily generate primers and probes, particularly EBV primers and probes, it would have been obvious to one of ordinary skill in the art and well within the skill of the art at the time the invention was made to have generated primers and probes identical and equivalent to the broadly claimed primers and probes that could be used to amplify and detect EBNA-1 expression. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers and probes in a kit for the benefits of convenience and cost-effectiveness for practioners in the art wishing to analyze EBNA-1 expression.

12. Claims 23 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over NCBI (Accession No. U21195) in view of Cheung and Zhang and further in view of Kievits.

The teachings of NCBI (U21195), Cheung and Zhang are presented above. The combined references do not teach incorporating a T7 polymerase promoter sequence into said primers.

Kievits teaches methods for amplifying nucleic acids by an isothermal enzymatic process referred to as NASAB. In this method, the primers are modified to include, at their 5' terminus, a T7 polymerase promoter sequence.

In view of the teachings of Kievits, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the BARF-1 primers so as to have included a T7 polymerase promoter at the 5' terminus in order to have generated primers which could be used to effectively amplify EBV BARF-1 target nucleic acids by the NASAB method

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

March 10, 2003

CARLA J. MYERS
PRIMARY EXAMINER